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PARKE-DAVIS

October 22, 1999

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Re: Docket No. 99D-2635: "Draft Guidance for Industry on ANDA's Blend Uniformity Analysis"

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Dear Sir/Madam:

This letter is in reference to the proposed Guidance that was published in the Federal Register, 64, (August 27, 1999), Docket 99D-2635.

It is agreed that blend uniformity analysis is valuable during the development and commercial validation phases of a product. However, the value of BUA testing is limited as a routine, in-process test for commercial batches and will add product cost without adding assurance to the overall quality of the product.

We believe the agency should either reconsider or modify the guidance set forth in this document for the reasons listed below:

1. The validation process ensures uniformity and homogeneity of the product;
2. BUA should not be required as a "formal" regulatory specification;
3. BUA requirements should reflect more stringent blending conditions practiced today;
4. Routine BUA is redundant in commercial batches where finished dosage units are tested routinely for drug uniformity as assurance of the drug homogeneity;
5. The Guidance should clearly state when BUA is not required;
6. Recommendations provided in the Guidance appear not to reflect current industry practices;
7. The intent of the last paragraph of Section II (Scope) should be clarified;
8. The recommendation against using two-tier (stage) testing in Section IV is inappropriate; and
9. The acceptance criteria in Section IV are statistically inappropriate.

The detailed discussions of each of these individual items are presented on the following pages.

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1. It is agreed that 21 CFR 211.110 (a)(3) establishes the requirement of in-process testing for adequacy of mixing to ensure uniformity and homogeneity. However, the validation process ensures uniformity and homogeneity, eliminating the need for testing BUA in every commercial batch manufactured using a validated process.

   - The blending step should be validated, as it may be responsible for causing variability. This is performed during development and validation, where BUA is used to assess blend variability.
   - Additionally, control procedures demonstrating the adequacy of mixing are interpreted to include 1) specific blend conditions, 2) qualified mixing equipment, 3) raw material physical properties, and 4) finished product tests for content uniformity. All these features are part of the Validation program, meeting 211.110 (a).
   - We do not interpret 211.110 (a) to mean that every commercial batch requires BUA in order to "establish control procedures for the adequacy of mixing." Adequacy of mixing is insured in the validation process. Once validated and shown to be consistent and accurate, routine BUA is redundant in commercial batches.

2. We do not agree that BUA is a "formal" regulatory specification (i.e. filed in an application). The FDA's 1993 "Guide to Inspections of Solid Oral Dosage Form Validation" addresses BUA strictly as a process validation issue. Under the section "Validation Issues for Oral Solid Dosage Forms," the entire theme of BUA is couched in the context of "sufficient trials to establish reproducibility of the process." The Guidance approaches BUA testing from the perspective of the company's validation protocol or SOP, neither of which should be required to be submitted to the Division.

   Furthermore, the FDA's "Guide to Inspections of Oral Solid Dosage Form Pre/Post Approval Issues for Development and Validation" (January 1994) addresses BUA in the following manner that is not addressed in the subject document:

   - BUA should be conducted during Development (Section III. Product Development, A. Reports, 3. In-process testing; Page 7).
   - BUA should be conducted during the Demonstration or Validation of the process (Page 18, section V. B. 3.).
   - The need for BUA should be based on the type blender used (precision vs. non-precision).

3. BUA requirements should reflect more stringent blending conditions. This allows for more control in the blending step with no improvement though conducting routine BUA. For example:

   - When the cGMP items in 21 CFR Part 211 were written, it was common for blending instructions to be more general. With these kinds of instructions, blending steps could easily contribute to in-process variability. However, in the past 10-15 years, specific instructions, automated timing, and raw material characterization (and controls) have eliminated blending step invariability.

   - During process development, the blending step is typically studied at different mixing conditions and controlled parameters are established. These are then developed into the guidelines and manufacturing instructions, which are validated prior to commercialization.

4. Routine BUA is redundant in commercial batches where finished dosage units are tested routinely for drug content uniformity as assurance of the homogeneity of the active ingredient. If BUA is required as a routine test for commercial batches, then some allowance should be made for parametric release. For example, finished product batches could be released on the BUA results for drug uniformity, and finished product content uniformity by USP should not be required.

5. The Guidance should clearly state when BUA is not required for intermediates, preliminary mixes or granulations, where subsequent blending steps will achieve uniformity.

6. Recommendations provided in the Guidance appear not to reflect current industry practices. For example:

   - NDA product manufacturers have manufactured drug products [with less than 50 mg active or less than 50% active ingredient(s)] for years without routine blend analysis and without any drug uniformity problems. Routine BUA will not change this.

7. Please clarify the intent of the last paragraph of the third paragraph of Section II (Scope). It states that the BUA in-process test may be deleted for commercial batches as long as "supportive information justifying that the test would not be considered necessary under cGMP" is provided. This seems to suggest that if adequate Process Development and Validation data exist demonstrating blending consistency, BUA would not be necessary for commercial production batches.

8. In the second paragraph of Section IV (Acceptance Criteria and Analytical Procedures), the recommendation against using two-tier (stage) testing is inappropriate. The USP allows testing of additional samples (n= 30) to obtain truer (i.e. more representative of the population) standard deviations of solid dosage forms. The Guidance should be consistent with the provisions of the USP on Content Uniformity.

9. In the second paragraph of Section IV ("Acceptance Criteria and Analytical Procedures"), the acceptance criteria are statistically inappropriate. The proposed criteria of 90-110% for the mean and RSD < 5.0% are not statistically sound. The lower limit of the mean minus two times the standard deviation is less than 85%. For example, the blend mean could be 91-92% with an RSD of 4.0-4.5% and individual values of 84% or less (n= 6 or 10). This is inconsistent with the USP's common acceptance criteria for finished product of 85-115% for each of 10 individuals, and differs from statements made in the July 1994 FDA "Inspection Guide on Oral Solid Dosage Forms" (Page.18, Granulation/Mix analysis during Validation).

   We agree with the statement that the blend acceptance criteria should "... allow compensation for any potential loss in blend uniformity during subsequent manufacturing steps..." However, to achieve this, the acceptance criteria should be tighter than USP, i.e. 90-110% for individuals, not the mean. This is an agreeable and achievable acceptable criterion established during Development and Validation.

Parke-Davis/Warner-Lambert appreciates the opportunity to comment on the Draft Guidance for Industry for ANDAs: Blend Uniformity Analysis. Should you have any questions regarding this submission, please contact me at 734/622-4938 or send a facsimile to 734/622-7890.

Sincerely,

Judith A. Strouss
Regulatory Scientist, CMC
Worldwide Regulatory Affairs

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